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1 Pioneering New Procedures in GI



1 Advancing Treatment for Fatty Liver Disease in Children

2 Comprehensive Care for Children with IBD

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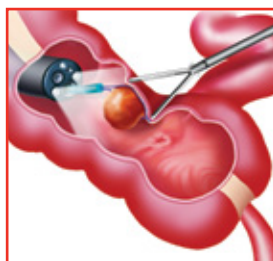
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Redefining Intestinal Surgery: Novel Devices, New Platforms

In an innovative collaboration between physicians and bioengineers at NewYork-Presbyterian Hospital and Weill Cornell Medical College, the development of medical technologies and procedure-based solutions is redefining intestinal surgery for some of the most significant clinical challenges. Led by Jeffrey W. Milsom, MD, Chief of Colon and Rectal Surgery at NewYork-Presbyterian/Weill Cornell Medical Center, the Minimally Invasive New Technologies (MINT) program is guiding an exciting new approach to colorectal surgery.



“This is a multidisciplinary assault on how you treat intestinal diseases,” says Dr. Milsom. “Considering that procedure-related treatments of many intestinal problems are, by and large, the only curative treatment, we’re looking at novel devices, more sophisticated imaging, and new biomaterials to make these procedures less invasive, more effective, and safer for the patient. Our goal is to dramatically shift the paradigm of how intestinal problems are treated.”

Combined endolaparoscopic surgery (CELS) is one of a series of procedures under study in the MINT program. “With CELS, you combine endoscopic and laparoscopic surgery, where endoluminally – within the channel of the intestine – we can safely remove, repair, and locally resect the offending lesion without the need for a major resection,” explains Dr. Milsom.

In a recent study of the long-term outcomes of patients undergoing CELS for benign colon polyps, Sang W. Lee, MD, Dr. Milsom, and their colleagues at Weill Cornell conducted a retrospective review from 2003 to 2012 of patients who had a large size polyp in a difficult location making it unsuitable for endoscopic removal. In these situations, patients typically undergo bowel resections. The researchers found the CELS procedure to be a safe and effective alternative to colectomy in all parts of the colon for treatment of benign polyps not removable with colonoscopy alone.

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Fatty Liver Disease in Children: Cause for Concern, Reasons for Hope

Joel E. Lavine, MD, PhD, Chief of the Division of Gastroenterology, Hepatology, and Nutrition at NewYork-Presbyterian/Morgan Stanley Children’s Hospital, has devoted his career to helping children with acute and chronic liver diseases. Nonalcoholic fatty liver disease is the most common cause of liver disease in children and its rise has been related to the increasing prevalence of obesity. In fact, according to recent studies, about one in 10

children in the United States are thought to have some form of fatty liver disease, a condition that stems from excess fat stored in the liver.

“In its mildest form, the liver appears to tolerate the extra fat, but in its most severe form – called non-alcoholic steatohepatitis, or NASH – the excess fat causes inflammation, scarring, and liver damage,” says Dr. Lavine, who has served as co-chair of the NIH-funded NASH Clinical Research

Network for the past 11 years. “The disease can lead to cirrhosis, liver cancer, and death, and also is related to type 2 diabetes, lipid disorders, and cardiovascular disease. Because they’re developing this problem at such a young age, many of these children have cirrhosis by age eight.”

More frequently diagnosed in boys, NASH is also more common in indigenous Americans, particularly Mexican-Americans. “If you are an obese Hispanic boy, 15 to 17 years old, your likelihood of having fatty liver disease is probably 80 percent,” says Dr. Lavine.

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Inflammatory Bowel Disease: Considerations for Pediatric Management

Over the past 40 years the incidence of inflammatory bowel disease (IBD) has increased dramatically, with 1.4 million people in the United States diagnosed with the disease, including some 100,000 children and adolescents.

“Lack of recognition and undertreatment of IBD in children can have serious consequences, including anemia that can affect cognitive function, poor growth, and issues with bone mineralization that can lead to unhealthy bones as they get older,” says Robbyn E. Sockolow, MD, Chief, Pediatric Gastroenterology and Nutrition at NewYork-Presbyterian/Komansky Center for Children’s Health. “Diagnosing IBD early is incredibly important.”

Dr. Sockolow and her team in the Pediatric Inflammatory Bowel Disease Center focus care on the whole child and not just their digestive tract. During the initial visit – either for a primary diagnosis, second opinion, or transition of care – the team conducts a multidisciplinary workup that may include examination of the child’s digestive tract, bone, eye, and skin health, as well as their mental health, family

dynamics, and support system. “The diagnostic evaluation is unique to that patient, as is their ultimate treatment plan,” says Dr. Sockolow.

Recognizing IBD is a lifelong diagnosis, the Center has recently established a transitional care program – the first one in the New York metropolitan area – that provides patients with the tools and resources that will prepare them to manage their own personal medical care. “We realize that these are young individuals who have a lifetime of opportunity,” says Dr. Sockolow. “We want to minimize their disease as an obstacle in their lives as much as possible.”

While focusing on the latest treatment and technologies to diagnose IBD, just as important the Pediatric Inflammatory Bowel Disease Center is involved in research that involves identifying genetic vulnerabilities and environmental risk factors, as well as patient registries that focus on long-term treatment outcomes and quality-of-life studies.

“Our biggest challenge is trying to further individualize patient care,” says



Dr. Robbyn E. Sockolow

Dr. Sockolow. “The presentation and intestinal issues within ulcerative colitis and Crohn’s disease vary considerably. Following the model of precision medicine allows us to design a diagnostic workup and a management strategy that is the most effective and least harmful to that patient. Our job is to keep the disease in remission to the point where it becomes an afterthought in our patients’ day. If we do our job well, they can go on to choose whatever they wish to be in their lives.”

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Redefining Intestinal Surgery

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“One of the problems with the colon is that it’s a very thin-walled structure,” says Dr. Milsom. “When you take off a tiny polyp there’s minimal risk. But when you take off a three or four centimeter polyp from the lining of the intestine you have a serious risk of perforation. If you are confident that the polyp is not cancerous, the CELS procedure allows you to safely and successfully remove the polyp. Our colorectal surgeons have treated close to 100 patients so far. The average length of stay for a CELS procedure is one day. The average length of stay for a patient who has the laparoscopic or open resection to treat the same problem is five days. This is a dramatic difference.”

Currently CELS is performed with anesthesia. Dr. Milsom and his colleagues are now perfecting an approach where patients can be sedated instead, as is done with a colonoscopy, and avoid a general anesthetic.



Dr. Jeffrey W. Milsom

Their ultimate goal, however, is to render CELS obsolete. “Scope instability within the intestine prevents clinicians from using endoscopes as true surgical tools,” says Dr. Milsom. “We have developed an adjunct device to current endoscopes that enables clinicians to create an isolated, stable, and manipulatable zone to enhance visualization and therapeutic capability of the scope. From this stabilized zone, we are developing a surgical platform so that the

endoscope becomes, in essence, a surgical tool enabling us to perform sophisticated surgical actions within the channel of the intestine without invading the patient’s abdomen.”

CELS is currently being used for benign polyps, but the MINT team is now developing similar approaches for the treatment of early cancers, strictures and narrowing of the intestine, fistulas, inflamed areas, bleeding, diverticulitis, abscesses that develop inside the abdomen as a consequence of various diseases, as well as for structural problems such as prolapse and volvulus.

Reference Article

Lee SW, Garrett KA, Shin JH, Trencheva K, Sonoda T, Milsom JW. Dynamic article: long-term outcomes of patients undergoing combined endolaparoscopic surgery for benign colon polyps. *Diseases of the Colon and Rectum*. 2013 Jul;56(7):869-73.

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Fatty Liver Disease in Children (continued from page 1)

Identifying a New Treatment

When Dr. Lavine first started investigating NASH nearly 20 years ago, with no treatments in sight other than lifestyle modifications for weight loss, he hypothesized that antioxidants might help heal the liver because fat appears to be a substrate for oxidants.

“I came to vitamin E based on what is thought to be the pathogenesis of the disorder, which is an accumulation of certain types of lipid in liver cells,” says Dr. Lavine. “One of the jobs of the liver is to take up excess energy and to store it. Most of the time that energy is stored as either a fat or as glycogen. Certain types of fat, however, are injurious to the function of the liver because it exposes the liver to oxidative stress.” Dr. Lavine began having some of his patients take vitamin E, and when he found that this reduced the levels of a serum enzyme, called ALT, which is typically elevated in children with NASH, he conducted the first clinical trial of vitamin E and NASH – a small pilot study with 11 patients – that was published in the *Journal of Pediatrics*.

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This piqued the interest of the National Institutes of Health, and with NIH funding, Dr. Lavine and researchers from eight other centers in the NASH Clinical Research Network undertook a more ambitious look at vitamin E in the largest ever placebo-controlled randomized trial of treatment for NASH using histology as an outcome measure. Nearly all of the 173 children in the trial were obese, and 121 had NASH, which can only be diagnosed with a liver biopsy. “Importantly, in these children, vitamin E reduced the signs of injury in the liver, particularly the massive swelling of the liver’s hepatocytes that is the major feature of NASH,” says Dr. Lavine. “Among children diagnosed with NASH at the beginning of the study, liver biopsies showed that 58 percent no longer had the disease by the end

of treatment, compared to 28 percent improvement in the placebo group. This was statistically significant. By reversing the damage, the cellular injury resolved.”

The findings, published in the *Journal of the American Medical Association* in 2011, solidified the role of vitamin E (now recommended at 800 IU daily of natural vitamin E) as a treatment for NASH along with lifestyle recommendations related to diet and exercise. Dr. Lavine also co-authored the adult trial of vitamin E for NASH in *The New England Journal of Medicine* in May 2010 that demonstrated the safety and efficacy of this treatment.

About the same time, a pilot trial by Dr. Lavine and his colleagues of the medication cysteamine, designed to treat the underlying metabolic cause of a rare disease called cystinosis, showed that it too worked in NASH. The NIH was again interested, and today, a time-released form of cysteamine is undergoing evaluation in a multicenter trial through the NASH Clinical Research Network. “When this current treatment trial is concluded in December of 2014, and when all 160 research subjects have completed one year of therapy, we will analyze the results to determine whether cysteamine is an effective treatment option, and if it appears superior or equivalent to vitamin E.”

Pioneering Work in NASH Continues

Having established the current therapy of choice for NASH, in children and adults, with a second therapy now in a full-scale NIH trial, Dr. Lavine has clearly established himself as a pioneer in the field. In 2012, he was asked to participate – the only pediatrician to do so – in the writing group for developing practice guidelines on the diagnosis and management of non-alcoholic fatty liver disease by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. These guidelines were published in June 2012 in each of the respective journals of these professional organizations.

This year, Dr. Lavine was invited to join a workshop sponsored by the FDA to establish clinical guidelines for industry on the development of drugs for fatty liver disease in adults and children, including clinical trial designs and endpoint



Dr. Joel E. Lavine

recommendations for demonstrating drug safety and efficacy.

Meanwhile, he and his colleagues in the NASH Clinical Research Network continue to collaborate on initiatives that will help address this growing concern in pediatric medicine. In addition to having developed major multicenter clinical trials for vitamin E and for cysteamine, the group has established a significant database of children who have undergone liver biopsies and been fully characterized prospectively. Members are now developing a study to determine the natural history of liver disease in children over the short and long term.

With the promise of continued NIH funding, the Network is pursuing the development of non-invasive biomarkers that would replace percutaneous liver biopsy. They will continue to evaluate potential therapies in clinical trials, including looking at antibodies to bacterial toxins in the gut to determine if neutralizing the toxins will decrease the irritation that results in liver inflammation.

Reference Article

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association – published June 2012 in *Hepatology*, *The American Journal of Gastroenterology*, and *Gastroenterology*.

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Advances in Adult and Pediatric Gastroenterology and GI Surgery

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